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Abstract: Objective Older adults are among the most frequent users of emergency departments (EDs). Nonspecific symptoms, such as fatigue and widespread pain, are among the most common symptoms in patients admitted at the ED. Interleukin 6 (IL-6) and tumor necrosis factor (TNF-) are inflammation biomarkers associated with chronic stress (i.e., dementia caregiving) and nonspecific symptoms. This study aimed to determine whether IL-6 and TNF- were prospectively associated with ED risk in dementia caregivers (CGs). Methods Participants were 85 dementia CGs, who reported during three assessments (3, 9, and 15 months after enrollment) if they had visited an ED for any reason. Cox proportional hazards models were used to examine the relations between resting circulating levels of IL-6 and TNF- obtained at enrollment and subsequent risk for an ED visit, adjusting for age, sex, use of ED 1 month before enrollment, physical and mental health well-being, body mass index, and CG demands. Results (log) IL-6 significantly predicted ED visits during the 15-month follow-up (B = 1.96, SE = 0.82, p = .017). For every (log) picogram per milliliter increase in IL-6, the risk of visiting an ED was 7.10 times greater. TNF- was not associated with subsequent ED visits. Exploratory analyses suggested that CGs with levels of IL-6 above the 80th percentile and experiencing high CG demands were at highest risk of an ED visit. Conclusions IL-6 levels and CG demands may be useful for predicting vulnerability for future ED visits. Although further studies should be conducted to replicate and extend these findings, interventions that successfully modify inflammation markers, including the underlying pathophysiology related to stress and/or comorbid illnesses, may be useful in preventing costly and detrimental outcomes in this population.

DOI: https://doi.org/10.1097/psy.0000000000000716

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ABSTRACT

Objective: Older adults are among the most frequent users of emergency departments (EDs). Nonspecific symptoms, such as fatigue and widespread pain, are among the most common symptoms in patients admitted at the ED. Interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) are inflammation biomarkers associated with chronic stress (i.e., dementia caregiving) and nonspecific symptoms. This study aimed to determine whether IL-6 and TNF-α were prospectively associated with ED risk in dementia caregivers (CGs).

Methods: Participants were 85 dementia CGs, who reported during three assessments (3, 9, and 15 months after enrollment) if they had visited an ED for any reason. Cox proportional hazards models were used to examine the relations between resting circulating levels of IL-6 and TNF-α obtained at enrollment and subsequent risk for an ED visit, adjusting for age, sex, use of ED 1 month before enrollment, physical and mental health well-being, body mass index, and CG demands.

Results: (log) IL-6 significantly predicted ED visits during the 15-month follow-up ($B = 1.96$, SE = 0.82, $p = .017$). For every (log) picogram per milliliter increase in IL-6, the risk of visiting an ED was 7.10 times greater. TNF-α was not associated with subsequent ED visits. Exploratory analyses suggested that CGs with levels of IL-6 above the 80th percentile and experiencing high CG demands were at highest risk of an ED visit.

Conclusions: IL-6 levels and CG demands may be useful for predicting vulnerability for future ED visits. Although further studies should be conducted to replicate and extend these findings, interventions that successfully modify inflammation markers, including the underlying pathophysiology related to stress and/or comorbid illnesses, may be useful in preventing costly and detrimental outcomes in this population.

Key words: biomarkers, emergency department, healthcare use, inflammation, older adults, stress.

INTRODUCTION

Caring for a loved one with dementia has been shown to increase risk for hypertension (1), cardiovascular diseases (2), and immune system dysfunction (3–5). Furthermore, the intensity of demands within caregiver (CG) populations has been shown to increase health risks, such that CGs with higher demands and mental health vulnerabilities are at greater health risk (2,6). Caregivers have been shown to have greater levels of stress and depression, and lower levels of subjective well-being, physical health, and self-efficacy compared with non-CGs (7). Caring for a family member with dementia is particularly stressful and burdensome. Dementia CGs spend more hours per week providing care and assisting with more activities of daily living (ADLs) and instrumental ADL relative to nondementia CGs (8). Dementia CGs have also reported higher emotional and physical strain, as well as financial hardship compared with nondementia CGs, with dementia status of the care recipient being a significant predictor of all three (8). Chronic stress experienced by dementia caregiving has been associated with impaired immune function (9). For instance, dementia CGs had worse immune response to influenza virus vaccination than matched non-CG control participants (4). In addition, women caring for a family member with dementia showed slower wound healing compared with controls (5). In another study, spousal dementia CGs experiencing chronic stress had reduced lymphocyte sensitivity to glucocorticoids and increased salivary cortisol compared with non-CGs (10). In addition, spousal dementia CGs have demonstrated higher levels of plasma interleukin 6

ADLQ = Activities of Daily Living Questionnaire, **BMI** = body mass index, **CVD** = cardiovascular disease, **IL-6** = interleukin 6, **MCS** = mental composite score, **PCS** = physical composite score, **TNF-α** = tumor necrosis factor α

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Received for publication August 2, 2018; revision received April 29, 2019.

DOI: 10.1097/PSY.0000000000000716

(IL-6) and D-dimer relative to non-CG controls (11). These stresses of caregiving, and in particular the health consequences that result, have the potential to place CGs at elevated risk for increased healthcare utilization, such as emergency department (ED) visits.

In 2014, Americans made 137.8 million visits to EDs, an increase of 14.8% since 2006 (12). The rate of ED visits was highest among individuals 65 years and older, at 538.3 visits per 1000 population (12). In 2016, the average cost of an ED visit was US $1917, and ED visits accounted for 23% of all outpatient medical expenditures, second only to outpatient surgeries (13). Nonspecific symptoms (14) rank among the top reasons for ED visits in all age groups. These symptoms include chest pain, abdominal and back pain, shortness of breath, and weakness (12,15). Because the origin of these symptoms is difficult to determine, prediction of who will make ED visits becomes challenging, as does treatment.

Recent evidence suggests that acute somatic experiences, such as pain (16), fatigue (17), aches and pains, and muscular tension (18), are associated with increases in inflammation biomarkers, including IL-6. IL-6 is a glycoprotein produced by a variety of lymphoid and nonlymphoid cells (19) and is easily determined by standardized assays. IL-6 is involved as a proinflammatory cytokine in the acute phase response to activating stimuli, such as infection or tissue injury (20). During the acute phase response, IL-6 can induce other acute phase proteins, such as fibrinogen, serum amyloid A, and C-reactive protein (21). It also plays a role in the activation of the hypothalamic pituitary adrenal axis and regulation of hematopoiesis (19). Indeed, acute psychological stress is known to produce a transient rise in peripheral cytokines (22–24), including IL-6 (25). Furthermore, chronic stress, such as experienced by dementia CGs, is associated with elevated IL-6 concentrations (11,26,27).

Several studies demonstrate that IL-6 contributes to nociceptor and central sensitization (28–30), and IL-6 levels increase after nerve injury (31,32). In individuals with lumbar radicular pain, higher serum IL-6 levels were associated with higher visual analog scale scores for low back pain and leg pain (33). Other research demonstrates that elevations in IL-6 are associated with "sickness behaviors," including complaints of headache, tired muscles, excessive fatigue, and self-reported fever (34). Therefore, we postulated that elevations in IL-6 might be a biomarker associated with symptoms driving visits to the ED.

In addition to explaining nonspecific symptoms, elevations in IL-6 levels have been implicated in risk for various health conditions and diseases (19) that may prompt ED visits. For example, elevated levels of IL-6 have been associated with future risk for stroke occurrence (35,36) as well as risk for other cardiovascular events, such as acute myocardial infarction, coronary heart disease, and congestive heart failure events (36). IL-6 is a significant predictor of all-cause and cardiovascular mortality (37). Higher circulating IL-6 levels have also been shown to predict disability onset among older adults (38), and among patients with community-acquired pneumonia, elevated IL-6 levels are associated with mortality risk (39).

Given the association of IL-6 levels with illness symptoms and diseases potentially associated with ED visits, we sought to examine whether IL-6 is a useful prognostic indicator of ED visits in a chronically stressed population of dementia CGs. We hypothesized that among dementia CGs, IL-6 would be prospectively associated with 15-month ED visit risk.

METHODS

Participants

Participants were 85 dementia CGs enrolled in the University of California San Diego (UC San Diego) Alzheimer's Caregiver Study; a clinical trial evaluating the effects of psychosocial treatments on psychosocial and cardiovascular disease (CVD) risk outcomes in CGs. Our laboratory has previously investigated psychological and biological mechanisms of CVD in CGs, including a clinical trial examining CVD risk (40). However, all participants in this study were new to our research and had not participated in any of our previous studies of CGs.

To be eligible, participants were required to be at least 55 years of age, providing at least 20 hours/week of in-home care to a spouse with a physician diagnosis of dementia, and endorse at least mild depressive symptoms (i.e., mild level of distress) as per a score of 5 or higher on the Patient Health Questionnaire 9 (41) at the time of enrollment. Caregivers were excluded if (*a*) either they or their care receivers were diagnosed with a terminal illness with a life expectancy of less than one year, (*b*) they lacked capacity to consent to the research project, (*c*) they were enrolled in another formal intervention study or were receiving psychotherapy to improve well-being or reduce distress, (*d*) they had blood pressure greater than 200/120 mm Hg (i.e., severe hypertension), or (*e*) they received a diagnosis of cancer, heart failure, myocardial infarction, or stroke in the 12 months before enrollment in the study.

All participants were recruited through outreach to local community agencies serving older adults and/or CGs, community health fairs, and through referrals from enrolled participants or dementia-specific agencies, such as the UC San Diego Alzheimer's Disease Research Center. Participants were enrolled between February 2015 and April 2017, and follow-up data collection was completed for all participants by July 2018. All CGs provided informed consent to participating in the study, which was approved by the UC San Diego Institutional Review Board.

Measures

Health Service Use

The use of emergency medical services and overnight hospitalizations were the key healthcare services assessed in the current study. Participants were asked at intake (baseline), 3-, 9-, and 15-month assessments if they had visited an ED or urgent care clinic (for themselves, not for their care receivers) or been hospitalized overnight during the previous assessment period (or up to 1 month before the baseline assessment). Because dates of ED or hospital visits were not requested, the date of the interview was used as the visit date. Visits to a walk-in clinic were not included as an emergency visit. Participants answering in the affirmative were given a score of "1," and participants who had not used these services were given a score of "0." The dependent variables in our analyses were either days from baseline to first ED visit or days to hospitalization.

Interleukin 6

Blood was collected at the baseline assessment by a research nurse in the CGs' homes through a 22-gauge forearm catheter after a 20-minute rest. We collected blood in EDTA tubes and later centrifuged for 15 minutes at 1732 relative centrifugal force at 4°C. Plasma was stored at −80°C until analyzed. The level of cytokine IL-6 was measured using an electrochemiluminescence-based multiarray method through the Quickplex SQ 120 system (Meso Scale Diagnostics LLC, Rockville, MD). We used the human proinflammatory panel-1 10-plex kits to detect two cytokines, IL-6, and tumor necrosis factor α (TNF-α). The system uses 96-well–based high throughput readout. Fifty microliters of prepared plasma samples or calibrator was added into the corresponding wells. The array was then incubated at room temperature with shaking for 2 hours and then washed three times with PBS containing 0.05% Tween 20. Thereafter, 25 μl of detection antibody solution was added with 2 hours of incubation at room temperature. After rinsing, 2× read buffer was added and the signals were detected by a Quickplex SQ

120 system. IL-6 concentrations in the samples were determined with MSD Discovery Workbench (Version 4) software, using curve fit mode. Intra- and interassay coefficients of variation were less than 10%.

Caregiver Physical and Mental Well-being

Caregiver physical and mental well-being was assessed using the physical composite score (PCS) and mental composite score (MCS) of short-form-12 (SF-12) health questionnaire (42). The SF-12 is a global health measure that assesses multiple areas of physical and mental health functioning regardless of age or disease. The PCS was created by summing factor-weighted scores across four functioning domains (i.e., physical functioning, role physical, which indicates the impact of physical health symptoms on everyday functioning, bodily pain, and general health), with higher scores representing better physical health. The MCS was created by summing weighted scores across the four domains of vitality, social functioning, role emotional, which indicates the impact of emotional symptoms on everyday functioning, and mental health scales.

Caregiver Demands

Functional impairment of care receivers was used as an indicator of CG demands. Caregivers were administered the Activities of Daily Living Questionnaire (ADLQ) (43), which contains 28 items assessing their care receivers' impairment in six areas encompassing self-care, household, employment, shopping, travel, and communication. All items are scored from 0 to 3, with higher scores reflecting greater impairment in that area of functioning. The total scale score expresses an individual's percent impairment in performing ADL.

Caregiver Demographics and Health Characteristics

We collected CGs' age, sex, and ethnicity/race. All participants were weighed and had height measured by the research nurse for body mass index (BMI) computation.

Statistical Analysis

Cox proportional hazards regression was used to determine the relationship between baseline continuous IL-6 values and prospective ED visit or hospitalization. Initial (unadjusted) models were used and included only (log) IL-6 as a predictor of outcomes. Subsequent models adjusted for the following demographic and health characteristics: age, sex, use of ED (or hospitalization) in the 1 month before enrollment, SF-12 PCS and SF-12 MCS, BMI, and CG demands. "Survival" time was the number of days between the baseline interview and the last interview or to the date of first ED visit/hospitalization. For variables in the model, hazard ratios (HRs) were computed as the primary measure of effect, along with their corresponding 95% confidence intervals (CIs). All statistical tests were two-sided with significance established at 0.05.

RESULTS

Table 1 reports descriptive statistics for the sample, including all variables used in the Cox regression analyses. At baseline, the sample of CGs ranged in age from 56 to 90 years (M (SD) = 74.20 (7.99) years) and was 80% female. The mean length of time for participation was 326.5 days, and only 3.5% participants had made an ED visit in the 30 days before enrollment. IL-6 demonstrated significant positive skewness and a log transformation was conducted to reduce skew and log-transformed IL-6 was used in all subsequent analyses.

Association of IL-6 With ED Use

Because one participant was censored at 72 days, before the earliest ED visit for the sample, this case was excluded from the Cox regression analysis of ED use, leaving a total sample size of 85 participants. Of these participants, 12 (14.0%) experienced an ED visit during the 15-month follow-up period. Results of our initial

TABLE 1. Sample Characteristics by 15-mo Follow-up ED Use

	With ED Visit (n = 12)		Without ED Visit (n = 74)			
Variables	n (%)	Range	n (%)	Range	t Score; χ^2	p
Age, M (SD), y	74.5 (9.6)	56–88	74.1 (7.8)	56–90	0.13	.90
Female	10 (83.3)		59 (79.7)		0.09	.77
Race/ethnicity						
White, non-Hispanic	9 (75.0)		60 (81.1)			.60*
Hispanic	2 (16.7)		7 (9.4)			
Black	1 (8.3)		3 (4.1)			
Asian/Pacific Islander	0 (0.0)		4 (5.4)			
BMI, M (SD), kg/m^2	28.9 (4.2)	21.6–35.3	27.1 (5.1)	18.3–45.0	1.17	.25
Previous ED visit	2 (16.7)		1 (1.4)			.05*
Hypertension	5 (41.7)		31 (41.9)		0.00	>.99
Heart disease	1 (8.3)		3 (4.1)			.46*
Diabetes	3 (25.0)		7 (9.5)			.14*
Liver disease	0 (0.0)		2 (2.7)			>.99*
Kidney disease	3 (25.0)		5 (6.8)			.079*
ADLQ score, M (SD)	72.8 (16.4)	42.3–98.7	66.1 (18.6)	16.7–96.0	1.18	.24
SF-12 PCS, M (SD)	42.7 (12.5)	23.2–63.5	50.2 (11.0)	21.1–67.0	−2.14	.035
SF-12 MCS, M (SD)	46.2 (12.6)	23.7–64.1	46.2 (8.9)	22.7–63.4	−0.02	.99
IL-6, M (SD), pg/ml	2.7 (4.3)	0.6–16.1	0.9 (0.7)	0.2–4.4	3.40	.001

ED = emergency department; M = mean; SD = Standard deviation; BMI = body mass index; ADLQ = Activities of Daily Living Questionnaire; PCS = physical composite score; MCS = mental composite score; IL-6 = interleukin 6; SF-12 = short form-12.

TABLE 2. Survival Analyses Model Results

	B	SE	Wald	*df*	*p*	HR (95% CI)
Age	0.03	0.05	0.29	1	.592	1.03 (0.93–1.13)
Female	0.65	0.95	0.47	1	.495	1.91 (0.30–12.28)
BMI, kg/m^2	0.02	0.07	0.11	1	.738	1.02 (0.89–1.18)
Prior ED use	3.06	1.17	6.86	1	.009	21.41 (2.16–212.00)
SF-12 PCS	−0.06	0.03	3.09	1	.079	0.94 (0.89–1.01)
SF-12 MCS	0.01	0.04	0.02	1	.888	1.01 (0.93–1.08)
ADLQ	0.04	0.02	4.12	1	.042	1.04 (1.00–1.09)
(log) IL-6	1.96	0.82	5.75	1	.017	7.10 (1.43–35.28)

SE = standard error; HR = hazard ratio; CI = confidence interval; BMI = body mass index; ED = emergency department; PCS = physical composite score; MCS = mental composite score; ADLQ = Independent Activities of Daily Living Questionnaire; IL-6 = interleukin 6.

Statistical results are for Cox proportional hazards model.

(unadjusted) Cox model showed that log IL-6 was significantly associated with ED visits (B = 2.53, SE = 0.67, HR = 12.52, HR = 3.36–46.64, $p < .001$). Results of the adjusted model are presented in Table 2. In this analysis, previous ED visit (B = 3.06, SE = 1.17, p = .009), CG demands (B = 0.042, SE = 0.021, p = .042), and IL-6 levels (B = 1.96, SE = 0.82, p = .017) significantly predicted ED visit. The HR data suggest that those CGs who had an ED visit 1 month before enrollment (n = 3) were at 21 times the risk of another visit during the follow-up period. For every point increase in CG demands, CGs experienced a 4.3% increased risk of an ED visit. Finally, each log picogram per milliliter increase in IL-6 was associated with a seven-fold increased risk of an ED visit.

In the primary analyses, TNF-α was not associated with ED visits and therefore not further examined in the exploratory analyses.

Exploratory Analyses

We conducted several follow-up analyses. First, we examined the interaction between CG demands and IL-6 levels to determine whether CGs at higher levels of IL-6 combined with higher levels of CG demands were more likely to use EDs. Because CGs with lower relative levels of IL-6 (e.g., 50th–60th percentile) were deemed less likely to make use of EDs, we sought to determine the value at which IL-6 crossed from "nonsignificance" to significance. We conducted two analyses in this regard. The first examined the interaction between linear ADLQ scores and log IL-6. Results of this analysis indicated that there was not a significant interaction (B = −0.048, SE = 0.067, Wald = 0.52, df = 1, p = .471).

We then also conducted a median split of IL-6, whereby two groups were created at the 50th percentile to denote "high" versus "low" IL-6 values. We then replicated our original Cox proportional hazards analysis using this IL-6_{50} variable in the model. If not significant, we continued these analyses by increasing our "high versus low" IL-6 split in 10-percentile increments, until IL-6 significantly predicted ED visits. Results of these analyses indicated that IL-6 became a significant predictor of ED visit at the 80th percentile (B = 1.72, SE = 0.69, Wald = 6.32, df = 1, p = .012), corresponding to an IL-6 value of 1.30 pg/ml (see survival plot in Figure 1).

Given the independent associations of both CG demands and IL-6 with ED risk, we conducted follow-up, exploratory analyses examining the combination of these factors for predicting ED visit. In this analysis, we examined the interaction between linear ADLQ scores and log IL-6. Results of this analysis indicated no significant interaction between CG demands (ADLQ scores) and IL-6. Then, as mentioned previously, we conducted exploratory analyses using the IL-6_{80} variable from the previous analysis to create "high" versus "low" IL-6 groups. We also created "high" versus "low" demand groups, whereby care receiver with mild or moderate ADLQ scores were "low" demand group, and those with "severe" functional disability were the "high" demand group. Then, we combined these factors to make four groups as follows: (*a*) low demand, low IL-6 (reference group; n = 30), (*b*) low demand, high IL-6 (n = 7), (*c*) high demand, low IL-6 (n = 39), and (*d*) high demand, high IL-6 (n = 9). We then repeated our original Cox proportional hazards model with this variable to predict ED visit. Unfortunately, coefficients did not converge for this model. Further exploration of the failure revealed this failure to converge was due to the fact that zero CGs in our reference group (low demand, low IL-6) experienced an ED visit during the 15-month follow-up. Raw data on the number of events per group were as follows: (*a*) low demand, low IL-6 (reference group; n = 0), (*b*) low demand, high IL-6 (n = 3), (*c*) high demand, low IL-6 (n = 5), and (*d*) high demand, high IL-6 (n = 4). Visual

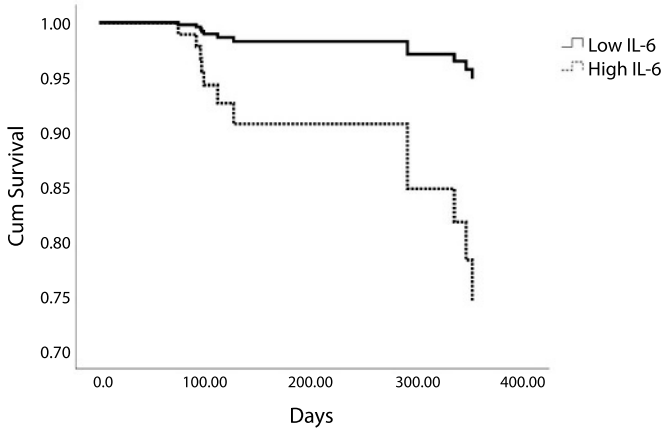

FIGURE 1. ED survival for CGs with "high" versus "low" IL-6. A total of 86 participants were available at the 3-month follow-up, 66 at the 9-month follow-up, and 45 at the 15-month follow-up.

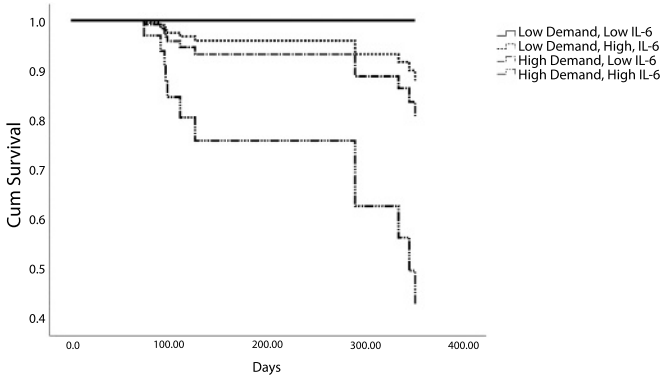

FIGURE 2. ED survival for interaction between CG demand and IL-6. A total of 86 participants were available at the 3-month follow-up, 66 at the 9-month follow-up, and 45 at the 15-month follow-up.

inspection of results showed a pattern of risk as follows: (*a*) lowest risk among individuals with low demand, low IL-6 (100% free of ED visit), (*b*) high IL-6, low demand (~88% free of ED visit), (*c*) high demand, low IL-6 (approximately 81% free of ED visit, and (*d*) high demand, high IL-6 (~43% free of ED visit). For graphical depiction of these results, see Figure 2).

Association of IL-6 With Caregiver Hospitalization

Three participants were censored before the earliest hospitalization event for the sample and were subsequently excluded from the Cox regression analyses, leaving a total sample size of 83 participants. Of these, five (5.8%) experienced a hospitalization during the 15-month follow-up period. Results of our initial (unadjusted) Cox model (B = 1.375; HR = 3.955, 95% CI = 0.268–58.277, p = .316) as well as the adjusted model (B = 0.773, HR = 2.167, 95% CI = 0.115–40.735, p = .605) showed that log IL-6 was not significantly associated with hospitalization. In this model, only female sex was significantly associated with hospitalization, whereby females were less likely to experience hospitalization than males (B = −3.068, HR = 0.047, 95% CI = 0.004–0.589, p = .018).

DISCUSSION

Results of this study support our hypothesis that circulating IL-6 levels significantly predict the risk for ED visit in CGs of those with dementia, independent of potential confounding factors including age, sex, recent ED visit, physical and mental well-being, and BMI. These results suggest that IL-6, whether associated with nonspecific symptoms or with some disease state, may predict ED utilization. In addition, CGs experiencing high demands (i.e., providing care for a care receiver with more severe functional disability) were at significant risk of experiencing an ED visit. In addition, because of our inclusion/exclusion criteria, our sample was relatively healthy and free of chronic illness. Therefore, our results are not restricted only to people experiencing specific diseases but more broadly relate to healthy individuals as well. Unlike for IL-6, TNF-α did not emerge as a predictor of ED visit. Although TNF-α is also a marker of systemic inflammation, one explanation for this discrepancy could be that TNF-α has much less consistently been associated with prefrailty and frailty in older adults than IL-6 (44). Frailty denotes a state of vulnerability to poor resolution of homeostasis after everyday stressors resulting in a cumulative decline in many physiological systems (45), thereby increasing the risk of ED visits (46).

These results are clinically interesting because IL-6 may serve as a predictor of ED use in an older adult population that has the highest utilization rate of these costly outpatient services. Exploratory analyses from this study indicated that IL-6 levels of 1.3 pg/ml or greater were prospectively associated with increased risk of ED visit. Although we urge caution, this may serve as a preliminary benchmark for clinical use of IL-6 in determining health risk in this population or as a benchmark for future research studies in determining risk in this and other older adult (non-CG) populations. Although IL-6 elevations could be due to several causes, valid prediction of who needs greater services could lead to better preventative care and reduce healthcare costs. Furthermore, CGs facing higher caregiving demands, such as taking care of care receivers with greater functional impairment, may be at even higher risk of ED visit. An exploratory analysis examining the interaction between CG demands (i.e., ADLQ scores) and IL-y6 was nonsignificant, suggesting that IL-6 may not exert stronger effects at different levels of CG demand. However, this interaction had low statistical power, and future studies with increased power should further examine this potential effect.

Multiple interventions have been shown to help decrease stress-related biomarkers and improve outcomes that often accompany high CG demand. For example, a behavioral activation intervention termed the Pleasant Events Program significantly reduced IL-6 levels and depressive symptoms among spousal CGs compared with an informational-support control condition (40). Another study found that CGs receiving a group cognitive-behavioral intervention experienced a significant reduction in daily salivary cortisol secretion compared with those in an educational intervention (47). Likewise, mindfulness-based stress reduction interventions may benefit CGs by reducing depression, CG burden, and increasing quality of life (48), and mindfulness-based stress reduction has been shown to significantly reduce IL-6 secretion in response to acute stressors (49). In addition to cognitive-behavioral interventions, respite services, such as home help and adult day care, may help reduce stress and alleviate CG burden (50). Future research should continue to examine the role of stress reduction interventions on inflammation biomarkers, such as IL-6, and determine the impact of these interventions on healthcare service use.

This study has several limitations. First, the CG population was racially homogenous (80.2% white) and consisted of adults 55 years and older, limiting the generalizability of our study.

Second, our study examined the relationship between IL-6 levels at baseline assessment to 15-month risk of ED visit. Greater understanding of ED risk may be gained from more frequent collections of IL-6 data. Next, ours was limited by a modest sample size and few ED and hospital visits. Next, IL-6 levels increase with age and measures are not standardized across laboratories and assessment methods, so cutoffs to identify individuals at risk may be different in younger populations and depend on the IL-6 assay used (51). These limitations make it necessary to interpret these results as preliminary, and replication of these results in larger and more diverse samples is necessary for adequate decision-making in a clinical context.

Finally, our study focused on spousal dementia CGs. On the one hand, although the mechanisms by which chronic stresses affect IL-6 may not be unique to dementia caregiving populations, there are unique elements involved in caring for a loved one with dementia. For example, the unique nature of caregiving requires ongoing care that makes avoidance or escape from the stresses of caregiving a difficult undertaking. The increased reliance of care recipients on their CGs over time makes respite increasingly difficult to achieve among caregiving populations. Indeed, the term "vulnerable CG" has been used to describe CGs who experience a high degree of demand and low degree of respite (52). Thus, additional research, possibly with other chronic stress populations including military personnel or those experiencing work stress (e.g., firefighters or police), should be conducted to fully understand the nature of these effects. Therefore, our results, particularly regarding the interaction between IL-6 and CG demand may not generalize to other populations, such as CGs of patients with other chronic diseases.

To summarize, higher IL-6 levels significantly predicted risk for ED visit in dementia CGs in a 15-month period adjusting for confounding factors including age, sex, recent ED visit, physical and mental well-being, and BMI. In addition, care receiver functional disability was also significantly associated with increased risk for ED visit. Exploratory analyses showed a possible interaction between these effects, whereby individuals with higher levels of IL-6 caring for care receivers with high functional disability seemed to be at the greatest risk for ED visit during the follow-up period. Future research should explore whether this relationship holds in samples of other age groups, non-CG populations, and determine whether early interventions can reduce both IL-6 and ED visit risk.

Source of Funding and Conflicts of Interest: This study was funded by the National Institutes of Health (NIH), via the National Institute on Aging (NIA) Grant RF1 AG015301 R25AG043364. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors report no conflicts of interest.

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Moderators of Response to Cognitive Behavior Therapy for Major Depression in Patients With Heart Failure: Erratum

In the article published in volume 81 of *Psychosomatic Medicine* on pages 506–512 (1), an error appeared in the author list. The final author, Michael W. Rich, was mistakenly listed as Michael W. Carney.

This has been corrected in the online version.

Reference

1. Smagula SF, Freedland KE, Steinmeyer BC, Wallace MJ, Carney RM, Rich MW. Moderators of response to cognitive behavior therapy for major depression in patients with heart failure. *Psychosom Med* 2019;81:506–12.